# Fact Sheet for Health Care Providers: Interpreting Zika MAC-ELISA Results

**February 26, 2016**

**Dear Health Care Provider:**

The U.S Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to authorize the use of the Centers for Disease Control and Prevention's (CDC) Zika IgM antibody capture ELISA (Zika MAC-ELISA) for the *in vitro* qualitative detection of human IgM antibodies to Zika virus. It is intended for use in sera or cerebrospinal fluid (CSF) when submitted with a patient-matched serum sample from individuals meeting CDC Zika clinical and epidemiological criteria for testing in qualified laboratories designated by the CDC. The test is intended for use as part of CDC's algorithm for Zika testing.

FDA issued this EUA based on data submitted by CDC to FDA, and on the U.S. Secretary of Health and Human Services' (HHS) declaration that circumstances exist to justify the emergency use of *in vitro* diagnostic tests for the detection of Zika virus and Zika virus infection. This EUA will terminate when the HHS Secretary's declaration terminates, unless FDA revokes it sooner.

The information in this Fact Sheet is to inform you of the significant known and potential risks and benefits of the emergency use of the Zika MAC-ELISA. For more information on this EUA, please see FDA's website at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm.

**Why is this test needed at this time?**

As of February 20, 2016, active Zika virus transmission is occurring in 29 countries and territories in the Americas. Among cases identified in 2015-16, it is believed that most transmission has occurred through mosquito bites and from mother to fetus. Sexual transmission has also been documented.

At this time, there are no FDA approved/cleared tests available that can detect Zika virus in clinical specimens in the United States. Therefore, CDC has developed this test to detect evidence of Zika virus infections in human sera and CSF. Current information on Zika virus infection for health care providers, including case definitions, is available at http://www.cdc.gov/zika/hc-providers/index.html. All information and guidelines, including those on Zika virus laboratory testing, may change as more data is gathered on this virus. Please check CDC's Zika Virus website regularly for the most current information (http://www.cdc.gov/zika/index.html).

If Zika virus infection is suspected based on current CDC clinical and/or epidemiological criteria, the Zika MAC-ELISA may be ordered. Please contact your state or local health department to facilitate testing. Anti-Zika IgM is typically detectable starting near day 4 post onset of symptoms and is reliably detectable for approximately 12 weeks following infection.

The results should be used in conjunction with clinical signs and symptoms, epidemiological information, and travel history to diagnose recent Zika virus infection. This test is authorized for use with serum, and with CSF (when submitted with a patient-matched serum sample).

As of February 20, 2016, serum is the priority specimen for collection and testing. Specimens should be collected with appropriate infection control precautions and according to the manufacturer's instructions for the specimen collection device. Sera should be collected in serum separator tubes and centrifuged after collection to reduce the likelihood of hemolysis.

**What are the symptoms of Zika virus infection?**

Most patients with Zika virus infection exhibit no symptoms. Symptomatic patients typically experience a mild illness characterized by fever, rash, joint pain, and/or conjunctivitis. The incubation period is unclear, but likely to be several days. Symptoms generally resolve on their own within a week.

Some reports from Brazil, a country with a large number of Zika virus cases, indicate a possible association between Zika virus infection in pregnant women and increased incidence of microcephaly (a birth defect characterized by small head size and impaired cranial and neural development in neonates) as well as other poor pregnancy outcomes. Only limited information is available regarding the association between Zika virus infection and microcephaly. The likelihood of a connection between the Zika virus infection and microcephaly, and if there is a connection, the point at which Zika virus infection may impact fetal development during pregnancy, are unknown.

There are also reports from Brazil of a possible association between Zika virus infection and increased incidence of Guillain-Barré syndrome.

As of February 20, 2016, there have been more than 90 confirmed cases of Zika virus infection in the United States. Most, but not all of these individuals have a recent travel history to areas with ongoing transmission. Public health officials have determined that Zika virus poses a potential public health emergency.

**What does it mean if the specimen tests positive for recent Zika virus infection?**

A positive test for Zika virus from the Zika MAC-ELISA indicates that anti-Zika IgM antibodies were detected in the sera or CSF of the patient. Confirmation of Zika MAC-ELISA positive or equivocal results requires additional testing by CDC or by qualified laboratories designated by CDC and in consultation with CDC, using the CDC-issued algorithm.

False positive serological results are possible (see next paragraph). Laboratory test results should always be considered in the context of clinical observations and epidemiologic information in making a final diagnosis and patient management decisions. Any positive test result for Zika virus infection should be reported to your local and state health departments. In the United States and its territories, positive results must be reported to CDC. For guidelines on Zika virus, please refer to http://www.cdc.gov/zika/hc-providers/index.html.

Positive and equivocal results are not definitive for diagnosis of Zika virus infection. False positive results may occur in some patients with recent, closely-related flavivirus infections, such as dengue infections. In patients who have received yellow fever or Japanese encephalitis vaccination, cross-reactive antibodies in both the IgM and neutralizing antibody assays may make it difficult to identify which flavivirus is causing the patient's current illness. It is possible that the Zika MAC-ELISA may generate positive results in patients with a history of non-Zika flavivirus infections. In the event of a false positive result, risks to patients could include any or all of the following: the impaired ability to detect and receive appropriate medical care for the true infection causing the symptoms, in the case of pregnant women, an unnecessary increase in the monitoring of a woman's pregnancy, or other unintended adverse effects.

It should be emphasized that the identification of possible Zika virus infection in a pregnant woman does not provide any definitive information about the state of health of the fetus. Many questions remain about the association between Zika virus infection in a mother and the impact to the child, such as timing, likelihood, and relevance of symptomatic vs. asymptomatic infection. Detection of Zika virus infection in the mother does not mean there is definite harm to the child.

**What does it mean if the specimen tests negative for recent Zika virus infection?**

A negative Zika MAC-ELISA result does not rule out Zika virus infection, particularly if testing is conducted less than 4 days after onset of symptoms (before IgM levels are expected to become detectable) or more than 12 weeks after the infection is thought to have occurred (as IgM levels are expected to drop). As with any test, providers must consider the patient's likelihood of exposure and the possibility of false laboratory results when making treatment or other patient management decisions. The possibility of a false negative result should especially be considered if the patient's recent exposures or clinical presentation are consistent with Zika virus infection and diagnostic tests for other causes of illness are negative. Conversely, a negative result in an asymptomatic patient with a lower likelihood of exposure (e.g., a short term traveler to an affected area) may suggest the patient is not infected.

Please refer to CDC guidance for Health Care Providers Caring for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure:

http://www.cdc.gov/mmwr/volumes/65/wr/mm6505e2er.htm?s_cid=mm6505e2er.htm_w

It is also important to note that Zika virus infection is not the sole suspected cause of microcephaly in neonates.

**Reporting Adverse Events**

You should report adverse events, including problems with test performance or results, to MedWatch at www.fda.gov/medwatch, by submitting a MedWatch Form 3500 (available at http://www.fda.gov/medwatch/safety/FDA-3500_fillable.pdf) or by calling 1-800-FDA-1088.

**Pregnant patients should receive the Fact Sheet for Pregnant Women: Understanding Results from the Zika MAC-ELISA. All other patients should receive the Fact Sheet for Patients: Understanding Results from the Zika MAC-ELISA.**

Contact Information for the Manufacturer:
CDC Emergency Operations Center (EOC)
1600 Clifton Road
Atlanta, Georgia, USA, 30329
Office phone: **CDC EOC (770-488-7100)**

Any significant new findings observed during the course of the emergency use of the Zika-MAC ELISA will be made available at http://www.cdc.gov/zika/index.html.